

WHAT IS CLAIMED IS:

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- 10 1. A method of screening for genes that modulate polyglutamine toxicity comprising:
- (a) providing a first animal expressing a polyglutamine sequence, wherein the sequence produces polyglutamine toxicity in the animal;
 - (b) breeding the first animal to a second animal, wherein the second animal has a marker sequence inserted into its germline, thereby producing progeny;
 - (c) screening the progeny for increased or decreased polyglutamine toxicity relative to the first animal thereby identifying a progeny having increased or decreased polyglutamine toxicity; and
 - (d) identifying one or more genes adjacent to or having an insertion of the marker sequence that confers increased or decreased polyglutamine toxicity in the progeny having increased or decreased polyglutamine toxicity.
- 15 2. The method of claim 1, further comprising step (e), identifying a mammalian homologue of the gene of claim 1.
- 20 3. The method of claim 2, wherein the mammalian homologue comprises a human homologue.
- 25 4. The method of claim 1, wherein the first and second animals are invertebrates.
5. The method of claim 4, wherein the invertebrates are of the genus *Drosophila melanogaster*.
6. The method of claim 1, wherein the marker sequence comprises a P element.
7. The method of claim 1, wherein the marker sequence comprises a polynucleotide sequence that disrupts or alters expression of one or more genes near the sequence.

8. The method of claim 1, wherein the marker sequence further comprises an expression control element conferring expression of the one or more genes near the marker.
9. The method of claim 8, wherein the expression control element increases or decreases expression of one or more of the near gene(s).
10. The method of claim 1, wherein the second animal is selected from a group of two or more animals having markers inserted into different locations of its genomic DNA.
11. The method of claim 10, wherein the second animal is selected from a group of 10 to 100, 100 to 500, or 500 or more of the animals.
12. The method of claim 1, wherein the second animal is selected from a library of animals having markers inserted at random locations of their genomic DNA.
13. The method of claim 12, wherein the library of animals is generated by random P element insertion.
14. The method of claim 1, wherein the polyglutamine sequence comprises a sequence having between about 35 to 50, or between about 50 to 100 glutamine residues.
15. The method of claim 1, wherein the polyglutamine sequence comprises a sequence having between about 100 to 150 glutamine residues.
16. The method of claim 1, wherein the polyglutamine sequence comprises a sequence having about 150 or more glutamine residues.
17. The method of claim 1, wherein the polyglutamine sequence further comprises a tag.
18. The method of claim 17, wherein the tag comprises an epitope tag.

19. The method of claim 18, wherein the epitope tag comprises a hemagglutinin sequence.
20. The method of claim 1, wherein the polyglutamine sequence is encoded by a polynucleotide containing a plurality of CAGs, CAAs or a combination thereof.
21. The method of claim 20, wherein expression of the plurality of CAGs, CAAs or combination thereof is conferred by a constitutive, regulatable or tissue specific expression control element.
22. The method of claim 21, wherein the regulatable element comprises an inducible or repressible element.
23. The method of claim 21, wherein the regulatable element comprises a GAL4 responsive sequence.
24. The method of claim 21, wherein the tissue specific element confers neural, retinal, muscle or mesoderm cell expression.
25. A progeny animal produced by the method of claim 1.
26. A transgenic animal comprising a transgene containing a plurality of CAG's and at least one CAA sequence encoding a polyglutamine repeat sequence.
27. The animal of claim 26, wherein the animal is an invertebrate.
28. The animal of claim 27, wherein the invertebrate animal is *Drosophila melanogaster*.
29. The animal of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 1:1 and 2:1.

30. The animal of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 2:1 and 5:1.
31. The animal of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 5:1 and 10:1.
32. The animal of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 10:1 and 50:1.
33. The animal of claim 26, wherein expression of the polyglutamine sequence is conferred by a constitutive, regulatable or tissue specific expression control element.
34. The animal of claim 33, wherein the tissue specific expression control element confers neural, retinal, muscle or mesoderm cell expression.
35. The animal of claim 33, wherein the tissue specific expression control element comprises an *Appl* or *rhodopsin 1* promoter or GLASS transcription factor element.
36. The animal of claim 26, wherein the polyglutamine sequence is between about 30 and 50 amino acids in length.
37. The animal of claim 26, wherein the polyglutamine sequence is between about 50 and 100 amino acids in length.
38. The animal of claim 26, wherein the polyglutamine sequence is between about 100 and 200 amino acids in length.
39. The animal of claim 26, wherein the polyglutamine sequence is between about 50 and 200 amino acids in length.
40. The animal of claim 26, wherein the polyglutamine sequence further comprises a tag.

41. The animal of claim 26, wherein polyglutamine toxicity is produced in one or more tissue or organs of the animal.

5 42. The animal of claim 26, wherein the animal further comprises a marker sequence inserted into its genomic DNA, wherein the marker is located adjacent to a gene or inserted into a gene whose expression or activity increases or decreases polyglutamine toxicity in the animal.

10 43. The animal of claim 42, wherein the marker sequence is near or inserted into a gene containing a J domain.

44. The animal of claim 43, wherein the gene is HDJ1.

15 45. The animal of claim 43, wherein the gene is TPR2.

46. The animal of claim 43, wherein the marker sequence is near an MLF gene.

✓ 47. A method for identifying a compound that modulates polyglutamine toxicity in an animal comprising:

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- (a) contacting the animal of claim 41 with a test compound; and
 - (b) determining whether the test compound increases or decreases polyglutamine toxicity in the animal, where increased or decreased polyglutamine toxicity identifies the test compound as a compound that modulates polyglutamine toxicity.
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48. The method of claim 47, wherein the compound is present in the animal's food or drink.

30 49. The method of claim 47, wherein the compound is administered to a tissue or organ of the animal.

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50. A method of producing a transgenic animal characterized by polyglutamine toxicity comprising:
- (a) transforming an animal embryo or egg with a transgene comprising a plurality of CAA and CAG sequences encoding a polyglutamine sequence having a length sufficient to produce polyglutamine toxicity in the animal produced from the embryo or egg; and
- (b) selecting an animal that exhibits polyglutamine toxicity in one or more cells or tissues
51. An isolated polynucleotide sequence having about 65% or more identity to a *Drosophila* TPR2 (dTPR2) sequence set forth as SEQ. ID NO:2 and which encodes a polypeptide that decreases polyglutamine toxicity, with the proviso that the sequence is distinct from the EST sequences set forth in Figure 11.
52. The polynucleotide sequence of claim 51, wherein the sequence encodes a subsequence of TPR2 that decreases polyglutamine toxicity.
53. The polynucleotide sequence of claim 51 operatively linked to an expression control element.
54. An isolated polynucleotide sequence that hybridizes under stringent conditions to a *Drosophila* TPR2 (dTPR2) sequence set forth as SEQ. ID NO:2, with the proviso that the sequence is distinct from the EST sequences set forth in Figure 11.
55. The polynucleotide sequence of claim 54, wherein the sequence comprises a polynucleotide having 20 or more contiguous nucleotides.
56. The polynucleotide sequence of claim 54, wherein the sequence comprises a polynucleotide having 50 or more contiguous nucleotides.

57. An isolated polynucleotide sequence having about 65% or more identity to a *Drosophila* MLF (dMLF) sequence set forth as SEQ. ID NO:4 and which encodes a polypeptide that decreases polyglutamine toxicity, with the proviso that the sequence is distinct from the EST sequences set forth in Figure 12.

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58. The polynucleotide sequence of claim 57, wherein the sequence encodes a subsequence of MLF that decreases polyglutamine toxicity.

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59. The polynucleotide sequence of claim 57 operatively linked to an expression control element.

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60. An isolated polynucleotide sequence that hybridizes under stringent conditions to a *Drosophila* MLF (dMLF) sequence set forth as SEQ. ID NO:4, with the proviso that the sequence is distinct from the EST sequences set forth in Figure 12.

61. The polynucleotide sequence of claim 60, wherein the sequence comprises a polynucleotide having 20 or more contiguous nucleotides.

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62. The polynucleotide sequence of claim 60, wherein the sequence comprises a polynucleotide having 50 or more contiguous nucleotides.

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63. A composition comprising a polynucleotide sequence encoding a human MLF polypeptide operatively linked to an expression control element in a pharmaceutically acceptable carrier.

64. A composition comprising a polynucleotide sequence encoding a human TPR2 polypeptide operatively linked to an expression control element in a pharmaceutically acceptable carrier.

- ✓ 65. A method of increasing survival of a cell having polyglutamine toxicity, comprising contacting the cell with an amount of TPR2 or MLF polypeptide sequence or a polynucleotide sequence TPR2 or MLF polypeptide to increase survival of the cell.
- ✓ 5 66. A method of decreasing apoptosis of a cell, comprising contacting the cell with an amount of TPR2 or MLF polypeptide sequence or a polynucleotide sequence TPR2 or MLF polypeptide to decrease apoptosis of the cell.
- ✓ 10 67. A method of decreasing polyglutamine toxicity in a cell having or susceptible to polyglutamine toxicity, comprising contacting the cell with an amount of J domain containing polypeptide, TPR2 or MLF polypeptide sequence, or a polynucleotide sequence encoding the J domain containing polypeptide, TPR2 or MLF polypeptide sequence to decrease polyglutamine toxicity in the cell.
- 15 68. The method of claim 67, wherein the cell is a neural, retinal, muscle or mesoderm cell.
69. The method of claim 67, wherein the toxicity is decreased by decreasing cell death or increasing cell survival.
- 20 70. A method of decreasing polyglutamine toxicity in a tissue or organ of a subject having or at risk polyglutamine toxicity, comprising contacting the tissue or organ with an amount of a J domain containing polypeptide, a TPR2 or MLF polypeptide sequence, or a polynucleotide sequence encoding the J domain containing polypeptide, TPR2 or MLF polypeptide, to decrease polyglutamine toxicity in the
- 25 tissue or organ of the subject.
71. The method of claim 70, wherein the tissue is brain, eye, muscle or mesoderm.
- ✓ 30 72. A method of decreasing the severity of a frontotemporal dementia, prion disease, polyglutamine disorder or protein aggregation disorder in a subject having or at risk

of a frontotemporal dementia, prion disease, polyglutamine disorder or protein aggregation disorder, comprising administering to the subject an amount of J domain containing polypeptide, a TPR2 or MLF polypeptide sequence, or a polynucleotide sequence encoding the J domain containing polypeptide, TPR2 or MLF polypeptide, to decrease the severity of the frontotemporal dementia, prion disease, polyglutamine disorder or protein aggregation disorder in the subject.

73. The method of claim 72, wherein the method comprises prophylactic administration.

74. The method of claim 72, wherein the disorder is a neurological or muscle disorder.

75. The method of claim 72, wherein the disorder impairs long term or short term memory or coordination of the subject.

76. The method of claim 72, wherein the disorder is characterized by the presence of protein aggregates, amyloid plaques, degeneration or atrophy in an affected tissue or organ.

77. The method of claim 72, wherein the disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jacob's disease (CJD), bovine spongiform encephalopathy, Huntington's disease (HD), Machado-Joseph disease (MJD), Spinocerebellar ataxias (SCA), dentatorubropallidoluysian atrophy (DRPLA), Kennedy's disease, stroke and head trauma.

78. The method of claim 72, wherein the severity is decreased by decreasing cell death or increasing cell survival.

79. The method of claim 72, wherein the severity is decreased by decreasing protein aggregation.